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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/016,686	11/02/2001	Alan Kingsman	674523-2012	4344

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EXAMINER	
HELMS, LARRY RONALD	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 04/13/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/016,686	KINGSMAN ET AL.	
	Examiner	Art Unit	
	Larry R. Helms	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *46-95* is/are pending in the application.

4a) Of the above claim(s) *46-50,55,56,58,59 and 69-95* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *51, 52, 53-54, 57, 60-68* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election with traverse of Group I, claims 52-66 drawn to nucleic acids, vectors and methods of producing a ScFv of SEQ ID NO:1 or encoding SEQ ID NO:5, in the paper filed 12/24/03 is acknowledged. The traversal is on the ground(s) that there should be no restriction between the SEQ ID Nos and there should be a species election and there are linking claims that should not be restricted to sequences and claim 51 should be included with Group I and claims 66 should be included with claims 67-68. This is found to be partially persuasive and claims 51 and 67-68 will be examined with Group I. As to the argument that there are linking claims none of Group I claims are linking claims, 51 which recites a nucleic acid is improper as it depends on a method claim. In addition, the restriction is not a species election because each ScFv is distinct because it has a separate SEQ ID NO and requires a separate search. It is acknowledged that method claims that are the same scope as the product claims be rejoined upon allowance of the product claims. As to the question of burden of search, classification of subject matter is merely one indication of the burdensome nature of the search involved. The literature search, particularly relevant in this art, is not co-extensive and is much more important in evaluating the burden of search. Clearly different searches and issues are involved in the examination of each group. For these reasons the restriction requirement is deemed to be proper and is made **FINAL**.

2. Claims 46-50, 55-56, 58-59, 69-95 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions. Applicant timely traversed the restriction (election) requirement in Paper filed 12/24/03.

3. Claims 51, 52, 53-54, 57, 60--68 are under examination and will be examined to the extent the nucleic acid is SEQ ID NO:1 or encodes SEQ ID NO:5.

Claim Objections

4. Claims 51, 52, 68 are objected to because of the following informalities:

A. Claim 51 is objected to as claiming a nucleic acid of the method of claims 46 or 47.

B. Claims 52-54, 57, 60-68 are objected to as depending on or having recited non-elected SEQ ID Nos.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 52, 60, 62, 64, 67-68 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claim 67 is indefinite for reciting "DAM" and "TAA" because these terms are laboratory designations and as such are indefinite.

b. Claims 67-68 are indefinite for reciting incomplete method claims which do not clearly set forth method steps and does not include a resolution step which reads back on the preamble of the claimed method. Merely stating that the "DAM is TAA" in

claim 67 or that the ScFV has SEQ ID NO:1 in claim 68 does not produce a ScFv. The claims should conclude with a step of producing a ScFv as required by the preamble, which recites "a process for preparing an ScFv".

c. Claims 60 and those that depend on claim 60 are indefinite for reciting "hybridizing" because it is unclear what full set of conditions are contemplated.

d. Claim 52 is indefinite for reciting "derivative". The claims are indefinite for reciting "derivative" as the exact meaning of the word is not known. The term "derivative" is not one which has a universally accepted meaning in the art nor is it one which has been adequately defined in the specification. The primary deficiency in the use of this phrase is the absence of an ascertainable meaning for said phrase. Since it is unclear how the ScFvs are to be derivatized to yield the class of derivatives referred to in the claims, there is no way for a person of skill in the art to ascribe a discrete and identifiable class of compounds to said phrase. Further, it is not clear whether the "derivative" of the antibody is formed by attachment of a detectable marker, therapeutic molecule, some other molecule or altering the amino acid sequence, for examples. In addition, since the term "derivative" does not appear to be clearly defined in the specification, and the term can encompass proteins with amino acid substitutions, insertions, or deletions, antibody fragments, chemically derivatized molecules, or even antibody mimetics. In absence of a single defined art recognized meaning for the phrase and lacking a definition of the term in the specification, one of skill in the art could not determine the metes and bounds of the claims.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claim 54, 60-66 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The general knowledge in the art concerning variants or homologues does not provide any indication of how the structure of one variant is representative of unknown variants. Reiger et al. (Glossary of Genetics and Cytogenetics, Classical and Molecular, 4th Ed., Springer-Verlay, Berlin, 1976) clearly define alleles as one of two or more alternative forms of a gene occupying the same locus on a particular chromosome... and differing from other alleles of that locus at one or more mutational sites (page 17). Thus, the structure of variant, homologues of nucleic acids are not defined. With the exception of SEQ ID NO:5 the skilled artisan cannot envision the detailed structure of the encompassed polynucleotide and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Thus, one of skill in the art would not understand that the applicant had possession of the claimed invention at the time the instant application was filed.

9. Claims 51-52, 54, 60-66 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated nucleic acid that is SEQ ID NO:5 or encodes the ScFv of SEQ ID NO:1 wherein the ScFv binds the 5T4 antigen as well as isolated vectors, isolated plasmids, and isolated host cells and methods of preparing a ScFv, does not reasonably provide enablement for a nucleic acid that encodes just any ScFv that binds to just any "DAM" or any variant, homologue, or fragment of a ScFv encoded by SEQ ID NO:1 or a variant, homologue or fragment of SEQ IFD NO:5 or any nucleic acid that hybridizes to SEQ ID NO:5 or encoding SEQ ID NO:1 or any vector, plasmid, or host cell comprising such. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The claims are broadly drawn to any nucleic acid that encodes any variant, homologue, derivative or fragment of SEQ ID NO:1 or any variant, homologue,

fragment, of derivative of SEQ ID NO:5 as well as molecules hybridizing to such and vectors and methods of preparing such molecules.

The specification teaches the production of a ScFv with sequence of SEQ ID NO:1 encoded by SEQ ID NO:5 (see Example 1). The ScFv binds the 5T4 antigen (see page 10, line 25-31). The specification contemplates using the vectors for production in human cells or organisms (see page 25 and page 34).

The claims are broadly drawn to any fragment of a ScFv or a fragment of a nucleic acid, which does not encode an entire ScFv or does not bind the 5T4 antigen.

It is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc Natl Acad Sci USA 1982 Vol 79 page 1979). Rudikoff et al.

teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. It is unlikely that proteins as defined by the claims which may contain less than the full complement of CDRs from the heavy and light chain variable regions, have the required binding function. The specification provides no direction or guidance regarding how to produce fusion proteins and antibodies as broadly defined by the claims. Undue experimentation would be required to produce the invention commensurate with the scope of the claims from the written disclosure alone.

Further, a fragment of the ScFv can be a CDR or a framework region. However, the language also reads on small amino acid sequences as well as single amino acids which are incomplete regions of the antibody. In addition, a fragment of a nucleic acid can be a single nucleotide. One of skill in the art would neither expect nor predict the appropriate functioning of the antibody as broadly as is claimed.

The claims are broadly drawn to a transgenic host cell. The state of the art at the time of filing was such that one of skill could not predict the phenotype of transgenics. For example, Overbeek (1994, "Factors affecting transgenic animal production," Transgenic animal technology, pages 96-98) taught that within one litter of transgenic mice, considerable variation in the level of transgene expression occurs between founder animals and causes different phenotypes (page 96, last paragraph). The art of transgenic animals has for many years stated that the unpredictability lies, in part, with the site or sites of transgene integration into the target genome and that "the position effect" as well as unidentified control elements are recognized to cause aberrant

expression of a transgene (Wall, 1996 Theriogenology, Vol. 45, pp. 57-68). The elements of the particular construct used to make transgenic animals are also held to be critical, and they must be designed case by case without general rules to obtain good expression of a transgene; e.g., specific promoters, presence or absence of introns, etc. (Houdebine, 1994, J. Biotech. Vol. 34, pages 269-287, specifically page 281). Furthermore, transgenic animals are regarded to have within their cells, cellular mechanisms that prevent expression of the transgene, such as methylation or deletion from the genome (Kappell, 1992, Current Opinions in Biotechnology, Vol. 3, pp. 548-553).

Well-regulated transgene expression is not frequently achieved because of poor levels or the complete absence of expression or leaky expression in non-target tissues (Cameron, 1997, Molec. Biol. 7, pages 253-265, specifically page 256, col. 1 -2, bridg. parag.). Factors influencing low expression, or the lack thereof, are not affected by copy number and such effects are seen in lines of transgenic mice made with the same construct (Cameron, 1997, Molec. Biol. 7, page 256, lines 3-9). With regard to the importance of promoter selection, Niemann (1997) states that transgenic pigs made with different promoters regulating expression of a growth hormone gene give disparate phenotypes - one deleterious to the pig, the other compatible with pig health (Niemann, 1997, Transg. Res. 7, pages 73-75, specifically page 73, col. 2, parag. 2, line 12 to page 73, col. 1, line 4).

Examples in the literature aptly demonstrate that even closely related species carrying the same transgene construct can exhibit widely varying phenotypes. Mullins

(1993, Hypertension, Vol. 22, pp. 630-633) states that not all animals express a transgene sufficiently to provide a model for a disease as the integration of a transgene into different species of animal has been reported to give divergent phenotypes. For example, several animal models of human diseases have relied on transgenic rats when the development of mouse models was not feasible. Mullins (1990, Nature, Vol. 344, 541-544) produced outbred Sprague-Dawley x WKY rats with hypertension caused by expression of a mouse *Ren-2* renin transgene. Hammer (1990, Cell, Vol. 63, 1099-1112) describes spontaneous inflammatory disease in inbred Fischer and Lewis rats expressing human class I major histocompatibility allele HLA-B27 and human β_2-microglobulin transgenes. Both investigations were preceded by the failure to develop human disease-like symptoms in transgenic mice expressing the same transgenes that successfully caused the desired symptoms in transgenic rats (Mullins, 1989, EMBO J., vol. 8, pages 4065-4072; Taurog, 1988, Jour. Immunol., Vol. 141, pages 4020-4023). Mullins (1996, J. Clin. Invest. Vol. 98, pages S37-S40) disclose that the use of nonmurine species for transgenesis will continue to reflect the suitability of a particular species for the specific questions being addressed, bearing in mind that a given construct may react very differently from one species to another. Thus, at the time of filing, the phenotype of a transgenic cell contained within any animal was unpredictable and could not be prepared for any species. Applicants can obviate this part of the rejection by amending the claims to recite the term "isolated" before the recitation, "construct, vector, plasmid, or host cell".

The claims are broadly drawn to any nucleic acid that is capable of hybridizing to the DNA of SEQ ID NO:5 or a variant, homologue, fragment, or derivative as well as a complement to such hybridized DNA and vectors and host cells comprising such and methods of producing a ScFv from such. It is well known in the art that not every nucleic acid that hybridizes will encode a ScFv or one that will bind to 5T4 antigen. It is also known that one could not produce a ScFv with just any DNA that hybridizes to or is complementary to the DNA of SEQ ID NO:5 (claim 66). The specification has not taught how to produce such ScFv with such nucleotide sequence in a host cell.

Therefore, in view of the lack of guidance in the specification and in view of the discussion above one of skill in the art would be required to perform undue experimentation in order to practice the claimed invention.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

11. Claims 51-52, 54, 60-67 are rejected under 35 U.S.C. 102(b) as being anticipated by Chaudhary et al (PNAS 87:1066-1070, 1990).

The claims recite a nucleotide sequence that encodes a ScFv that binds to a TAA and is a encoded by a variant of SEQ ID NO:1 or a variant of SEQ ID NO:5 hybridizing molecules and promoters, vectors, host cells and method of producing an ScFv.

Chaudhary et al teach nucleic acids, vectors, promoters, host cells, and method of producing a ScFv that binds a TAA. Because the claims recite a variant the art reads on the claims. In addition, the non-coding strand would inherently hybridize to the coding strand and thus meet the limitation of claim 60. In addition, the coding strand would hybridize to the non-coding strand and Chaudhary teach the coding strand in a vector thus meeting the limitation of claims 62 and 64.

12. Claim 60 is rejected under 35 U.S.C. 102(b) as being anticipated by The Promega 1993/94 catalog of nucleic acids,page 215-216.

The claim has been described supra.

The Promega Catalog teach random primers that would hybridize to SEQ ID NO:5 or a variant or to the DNA encoded by a variant of SEQ ID NO:1.

13. Claims 51-52, 54, 60-67 are rejected under 35 U.S.C. 102(e) as being anticipated by Chester et al (US Patent 5,876,691, filed 7/96).

The claims have been described supra.

Chester et al teach nucleic acids, vectors, promoters, host cells, and method of producing a ScFv that binds a TAA of CEA. Because the claims recite a variant the art reads on the claims. In addition, the non-coding strand would inherently hybridize to the coding strand and thus meet the limitation of claim 60. In addition, the coding strand would hybridize to the non-coding strand and Chester et al teach the coding strand in a vector thus meeting the limitation of claims 62 and 64.

14. Claims 51-54, 57, 60-68 are rejected under 35 U.S.C. 102(a) as being anticipated by Kingsman et al (WO 98/55607, published 12/10/98).

Claims 51-52, 54, 60-67 have been described supra. Claims 53, 57, 68 recite wherein the sequence is SEQ ID NO:5 and 1 and a method of producing a ScFv of SEQ ID NO:1.

Kingsman et al teach the Scfv of SEQ ID NO:1 encoded by SEQ ID NO:1 as well as promoters, vectors, host cells and method of producing such (see entire document, especially Figure 1A).

Conclusion

15. No claim is allowed.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D, whose telephone number is (571) 272-0832. The examiner can normally be reached on Monday through Friday from 7:00

am to 4:30 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, can be reached at (571) 272-0871.

17. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Fax Center telephone number is 703-872-9306.

Respectfully,

Larry R. Helms Ph.D.

571-272-0832